A RESUME OF THE PHYSIOLOGY OF THE KIDNEY, WITH A VIEW TO THERAPEUTICS.[1]

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A review and, as far as possible, a fair summary of the state of our knowledge of the physiology of the kidney seems to me to be quite worth while, especially in view of its great importance to those who are combating disease; because of the very rapid advances and the many changes which our knowledge of the functions of the kidney, synthetic, analytic, and secretory, have recently undergone; and because the old-time theories proposed by Ludwig and Heidenhain are, with this increase in knowledge, being gradually modified by their respective followers, and in many important points approaching each other; though it must be admitted that the theory of Ludwig, as was to be expected from its inherent simplicity of explanation, is being widely deviated from. I will discuss at the close of the paper the probable constructive lines for a new theory. First, I wish to adduce the important facts.

I. The Internal Secretion. The chief arguments in favor of this theory suggested by Brown-Séquard are as follows:

1. It has been observed in both men and animals that occlusion of both ureters leads but slowly to death (men have lived frequently fourteen to sixteen days), and that death ensues in man (it is harder to judge of this in animals) without marked symptoms of uremia, often with hardly a symptom that could be classed as uremia. In Fowler's summary of 93 cases, more than 66 per cent. showed no marked uremic symptoms. On the other hand, in animals and in man, when accidentally a single functional kidney has been removed, death occurs more rapidly (four to six days in man), though at least 1 case is on record in which a man lived eleven days; nor do all cases show marked uremic symptoms, though they are more common than in the first group. There is, however, it must be noted, a very marked difference in the severity of the operations for ureter closure and kidney removal in animals, and in man the ureters have rarely been closed by operative interference, and then only in severe operations. This fact must be seriously considered when considering the value of the differences between the two groups of cases.

2. Bradford and others have noted very marked wasting of the body and increased loss of nitrogen accompanying the polyuria which supervenes when five-sixths of the kidneys are removed. This, too, may be ascribed to an internal secretion.

3. The pharmacological experiments of Brown-Séquard and

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others who tried to reduce an impending or existing uremia produced in animals by double nephrectomy by injections of (*a*) glycerin extract of kidney, or (*b*) defibrinated blood from normal animals, taken either from kidney veins or the general circulation. Brown-Séquard himself was the first to experiment with the glycerin extract. His experiments seem to have been few in number and are not reported in detail. He himself subsequently appears to place more reliance on his pupils' work and upon general considerations such as the above. Ajello and Parascandalo operated on twelve dogs who died in from four to forty-eight hours; of ten other dogs which, after similar operation received glycerin extract injections, one lived four days, six others three days, the other three died in from forty-eight to fifty-two hours. This is not very convincing, especially when the controls died so early—four hours even; much longer survivals than forty-eight hours have occurred in similar experiments reported by other observers. Their rabbit experiments are not more convincing. The work of Meyer, a pupil of Brown-Séquard, whose work is considered by the latter as conclusive, is still less satisfactory. In one series of experiments he chose the cessation of dyspnœa, as recorded graphically, as a sign of improvement. Neglecting the fact that the method of recording might lead to deception, the criticism used is hardly a satisfactory one, as is urged with reason by Tigerstedt and Lewandowsky. His experiments are only five in number—three dogs and two rabbits. He used for injection blood of normal animals. Meyer, and also Vitzou, carried on a series of experiments in which the length of postoperative life with and without injections of blood was compared. Animals receiving injections had certainly longer postoperative lives, but that this was due to an internal secretion is rendered doubtful by the experiments of Chatin and Quinard, who showed the blood serum, which one would expect to contain the secretion, had absolutely no effect in prolonging the animals' lives. They have a longer and more complete experimental series than have either of the others. It seems that either the internal secretion must be carried by the corpuscles or that the corpuscles aid in prolonging the postoperative lives, if, indeed, they were prolonged in the experiments reported above.

4. Therapeutic experiments with extracts of kidney on uremic and nephritic persons are reported as successful by Dieulafoy, Tiessier and Frankel, Jacquet, Concetti, and Chiperowitz. A careful analysis of such cases as I have been able to see are not convining. Comparatively sudden changes for the better are not rare in nephritis. The treatment seems to have fallen into disuse since, in the literature available, I have found no reference to it since 1898.

5. As shown by several observers, uremia has supervened in nephritis without evident nitrogen retention. This is an unexplained fact.

I think it unnecessary to consider the experiments of Tigerstedt and Bergmann, so completely nullified by those of Lewanowski, nor the evidence that some have tried to deduce from the variations in hemolytic and toxic properties of serum and urine in cases of nephritis.

To sum up, I think that Brown-Séquard's suggestion has been rendered not more, but rather less, plausible than when first communicated. Great loss of functional kidney substance does lead to an abnormal metabolism, but this by no means proves an internal secretion.

II. SYNTHETIC AND ANALYTICAL FUNCTIONS. The mention of the paper of Barcroft and Brodie, who showed that increase in the excretory function of the kidney led to an increased consumption of oxygen and increased giving off of carbon dioxide in the blood, leads me to speak of the other known chemical activities of the kidney.

1. *Synthetic.* I need but to recall that the kidney can synthetize hippuric acid from glycerin and benzoic acid, salicyluric acid from salicylic acid and glycine. Also carbonic acids of many other nuclei in addition to that of the benzene nucleus, such as, furan, thiophene, and pyridin can be excreted in similar combinations. That this is a function of the kidney and doubtless of the tubules, has been still further confirmed by the success of Abelous and Ribaut in isolating to a certain extent the ferment responsible therefor.

2. *Analytic.* Schittenhelm has distinctly shown that the kidney contains a ferment which is able to split uric acid into urea, and also ferments which desamidize and oxidize other purin bodies. It is possible also that kreatinin, which, as Landois showed, is toxic with symptoms resembling uremia, may be formed by dehydration in the kidney from the nontoxic kreatin. Doubtless other synthetic and analytic functions will be discovered, and it may well be that their disturbance will, in large part, explain the causation of uremia.

III. TUBULAR EXCRETIONS. Nevertheless, these functions are, on the whole, subordinate to the main function of the excretion of urine.

1. The paper of Ebstein and Nicolaier, and, more convincingly, those of Sauer and of Anten, show that uric acid is excreted by the cells of the convoluted tubules and also, possibly, by those of the ascending loop of Henle. Undoubtedly those cells which carry on synthetic and analytic activities will also cast their products into the tubular lumen, and we will not be far astray if we localize these functions also in the tubule. Some experiments performed by Tropp show that such a synthesis as that of hippuric acid is not accompanied by any increase in water excretion. I have lately tried in three experiments to find an increased flow of urine when uric acid is secreted in large quantities, but as yet all experiments have been completely negative. Greatly increased uric acid excre-

tion was accompanied by a decrease, not an increase, in water. Phloridzin is known to be a poison which attacks the tubules, and some evidence exists that the passage of dextrose into the urine after the use of this poison is accompanied by loss of water. This may also be true of such poisons as cantharidin and possibly calomel. The pigments are also probably excreted by the cells of the convoluted tubules, as injected foreign pigments have been shown to be by Hober and Königsberg.

Attention must also be called to the fact that the urine leaving Bowman's capsule is alkaline, as shown by Dresser, while in the convoluted tubules it becomes acid. This is probably due to an increase in the free hydrogen ions, owing to the passage of CO_2 which, in the experiment of Barcroft and Brodie, does not appear in the venous blood in proportion to the oxygen lost by the arterial blood.

2. The recent papers of Bainbridge and Beddard and of Cullis and Brodie, if confirmed, as is probable they will be, will prove that the tubules in the frog, at all events, can excrete water, urea, chlorides, sulphates, probably kreatinin and phosphates, and dextrose when there is hyperglycemia or when poisoned with phloridzin. Caffeine sodium benzoate also seems to stimulate to excretion (note this body contains two substances which should influence tubules). It is, of course, doubtful how far we can apply to man results obtained on frogs in which the relations of the blood supply are so different, the tubules having, as well as the arterial, a secondary venous blood supply from the lower limbs; still, if we do so, the following points in the experiments of Cullis are of importance: the tubules on a venous supply did not excrete except when stimulated; neither phosphates, chlorides, nitrates, nor sulphates acted as such a stimulant; urea was a weak or doubtful stimulant, while phloridzin and caffeine sodium benzoate were the successful stimulants. The work of Loewi and Schmid would also go to show that sugar is excreted by the tubules when poisoned with phloridzin. The increase in urine flow accompanying it they consider to be due to a prevention of water absorption.

Accepting the observations of Cullis and Brodie on frogs, it is apparent that the diuretic salts, sulphates, phosphates, carbonates, if in excess in the body, must be got rid of by the glomeruli. This is the view most generally accepted, though Meyer and others do not fully concur in it. Before, however, we consider the excretion of salts, I wish to draw attention to the fact that under any but the most extreme experimental conditions an excess of such salts cannot occur in the blood without at once introducing osmotic pressure differences between the blood and the tissues, and that these are at once done away with, first, by water passing into the blood; and, second, by salts passing into the tissues. Very rapid salt absorption will lead to hydremia.

3. *Inorganic Salts and Urea.* The following facts are to be noted in regard to urea and nitrogen excretions: Urea occurs in normal urine in higher concentration than in the blood plasma (100 c.c. of urine often contains as much urea as 2 liters of plasma).

The more rapid the flow of urine, in general, the smaller the percentage of urea; the greater the daily quantity, the lower the percentage; but the total daily amount of urea will vary only with the daily nitrogenous katabolism.

Especially in cases of nephritis, the output of urea does not necessarily keep pace with its intake nor with katabolism (heaping up of non-coagulable nitrogenous bodies has been shown to occur in the blood), and this in cases in which water excretion appears normal; in other words, nitrogen retention with normal water excretion. The cause of such retention does not necessarily reside in an inability on the part of the kidney to excrete urea, though it may be so in some cases. Such nitrogen retention may persist for a long time (as in a case reported by Draper, for thirty days, and amount to 146 of nitrogen) without uremic symptoms.

4. *In regard to chlorides:* retention of chlorides in nephritis leads almost at once to a retention of water. Retention of salt has amounted to 40 to 50 grams, and was accompanied by proportionate increase in œdema. So many cases are now on record in which chloride retention has been shown to be the cause of water retention, that Marie has been led to frame the following hypothesis: that at first, on retention occurring the tissues are able to fix and retain a certain amount of chloride; when this is surpassed, water retention must occur. With restored chloride excretion, water also is given off. But the failure to excrete chlorides is rarely or ever absolute; retention occurs only above a certain daily intake. If the salt intake be reduced below this limit chloride elimination occurs, and, with it, water (Widal, Halpern, Claus, Plaut, and Reach). Increase in intake sometimes seems to hinder excretion.

5. *Sulphates and phosphates* may, like the chlorides, vary independently of their intake, and also of the nitrogen output, or temporarily of the water. Such massive retentions as are reported for chlorides, however, do not occur, and, as a whole, their daily amounts vary with the food intake and daily katabolism.

All these salts are present normally in the urine in larger amounts than in the plasma, but the more rapid the urine excretion, the lower their percentage, until it may happen that in extreme cases traces alone of chlorides occur. The urine may also come to have a higher freezing point than the plasma, that is, contain a much lower salt percentage (Dreser, Brodie, Henderson, Frey, etc.).

The excretion of a urine with a lower salt content than the normal blood for a long time—several hours in animal experiments—as shown by Achard and Paisseau, Reichel, Brandstein, and others, causes definite degenerate changes in the convoluted epithelium.

Leopold has also shown recently (his paper much needs verification) that feeding to rabbits and dogs a not excessive amount of salt daily (rabbits from 0.05 to 1 gram), also led to changes in these same convoluted tubules. He also showed that the changes caused by phosphates were much more marked.

6. *Water.* In regard to the excretion of water even the most ardent advocates of the secretory activities of the tubules suggest the glomerulus as the site of the main water excretion. The phylogenetic development of the kidney suggests it; the glomerulus at first is projected into the body cavity near the inner end of the neophrostome, whose mouth is lined with cilia. It must also, however, be noted that it was then the main, if not the sole, excretory apparatus for other body waste. The histology of the kidney suggests it. The afferent vessel to the glomerulus is larger than the efferent; the efferent vessel breaks up about the lower tubules to form a second capillary network. Hence the blood pressure in the glomerulus must be high; the pressure in its capillaries higher than elsewhere in the body. The epithelium of the glomerulus is thin and very flat, and probably syncytial. It is not gland-like in appearance.

Increased water production is favored by (*a*) an increase in blood flowing through the kidney (Starling, etc.). This must be qualified by the reservation that the blood may not be too concentrated. Observations are on record in which, though the blood flow through the kidney increased when caffeine was given, yet little or no secretion occurred, and it has been shown that in these cases the percentage of water in the tissues was low (Henderson). (*b*) Increase of blood pressure from the arterial side, if not accompanied by a decreased flow through the organ, increases the flow. Impeding venous outflow decreases water excretion. There is a certain minimum blood pressure below which no urine is excreted. This minimum varies with the composition of the blood—the more hydremic the blood, the lower the minimum; it is probably between 30 to 40 mm. Hg. in man (Starling, Henderson). Caffeine has been shown to dilate the vessels of the kidney, and, at the same time, by its heart action the blood pressure does not fall (Loewi, Brodie, etc.). (I believe that only when the kidney vessels are greatly dilated before injection does dilatation not occur.) That means an increased flow of blood through the kidney under equal or increased pressure. It may fail as a diuretic if the patient be poor in water. Other purin bases act as diuretics in the same way. As pointed out above, caffeine may possibly lead to increased activity of the tubules as well. Digitalis is not a diuretic in normal individuals, but is invaluable in those cases in which the circulation is poor. With improvement in the circulation comes diuresis. It may fail, of course, in those œdematous cases in which the œdema is due to chloride retention. Mercury salts, as pointed out above, are poisons for the tubule cells, and no doubt act as such. Hydremia is apt to dilate the vessels of the kidney, but is not constant in its action. (*c*) The presence in the blood of increased amount of salts, with high osmotic equivalents, sulphates, phosphates, carbonates, as well as the occurrence in increased amounts of salts with not such high osmotic equivalents, chlorides, dextrose, nitrates, increase the flow. All these act largely, first, by increasing the water content of the blood; second, by carrying water with them into the tubules and retaining it there (Loewi, etc.); and third, evidence is also to be found in many papers that salts in exeess may also cause a local dilatation of the vessels of the kidney (Magnus, Brodie, etc.). (*d*) The addition, by the tubules, of dextrose or other crystalloids increases the flow.

Reversal of the above conditions, decrease in blood flow, in the amount of salt in blood stream, etc., will decrease the flow of urine.

Finally, in nephritis, damage may lead to a primary inability to excrete water, and, on account of osmosis, salts must be retained, and thus greatly decrease the amount of urine.

Having thus briefly, and necessarily imperfectly, but I hope not unjustly, reviewed the facts in regard to kidney function, may I be allowed briefly to sum up the facts as they stand, and contribute in a word or two a picture of the production of urine. First, the cells of the tubules do undoubtedly excrete urates, hippurates, pigments, and, possibly, creatinin. They are permeable, and, in the frog, as in man, may excrete water, chlorides, urea, phosphates, sulphates, under stimulus, and, under still more abnormal circumstances, dextrose (phloridzin hypercemia). Second, the urine leaving the tubules, though usually more concentrated than the plasma in salts and urea, under a rapid flow more closely approximates to it in salt composition, and may even in some cases become much more dilute than the plasma, as in, experiments spoken of above and in diabetes insipidus. The first of these facts, great concentration, may be explained by very great water absorption by the tubules, which, there is evidence to show, does occur. The second, only by very greater absorption of salts by the tubules, and this is especially hard to understand in cases such as diabetes insipidus, in which the body really seems to need water. This necessary supplementary explanation, taken in conjunction with all our more recent knowledge of living animal membranes, many subsidiary difficulties not mentioned in the paper, and facts in regard to the definite excretory functions of the tubule spoken of, so overloads and modifies Ludwig's conception of the excretion of urine as to make it no longer tenable, even if we make, as has been pointed out to be necessary, the modification of understanding for "filtration" "diffusion modified by pressure." Then must we, with Heidenhain, say the glomerulus and tubules secrete. It appears to me to be a matter of definition. Heidenhain, when he said secrete, meant, I think, secretion, such as is carried on by other glands.

Let us take a typical secreting gland, such as the submaxillary, and see what secretion means in its case. It is, first, supplied with nerves, stimulation of which causes a flow of secretion even without increased blood flow. The kidney appears to have none such. Such a gland, on appropriate stimulation, nervous or chemical, secretes, and even against considerable pressure, even if the blood supply be poor; in the extreme case even if it be absent. The kidney in rabbits fails absolutely to secrete if the blood pressure be lower than 30 mm. Hg. and the blood normal. Caffeine is looked upon as the most efficient chemical stimulus we have (salts and water cause changes in the blood and urine which may greatly alter the conditions); yet, as I have shown, when the body is poor in water, caffeine fails as an excitant to secretion, though it brings about the necessary vascular changes. Such a gland, furnished with normal blood, will secrete when stimulated against a pressure many times the blood pressure of its vessels. This the kidney fails to do, although the glomerulus does not alone excrete, and there is no very great distance from the convoluted tubules to the ureter, but here, it must be noted, that the excretion of the tubules is not necessarily accompanied, as shown by Tropp and myself, to be accompanied by much water. Change in renal blood pressure is exactly and instantly followed by the pressure in the ureter, and a fair flow of urine, with a high blood pressure, will give a greater ureter pressure than a faster urine flow with a low blood pressure. We have, therefore, in the kidney a different type of secretion. Why not drop the word, with its associations, and say excretion?

If both these old theories have proved to contain fallacies, is there any theory which can be propounded to explain the production of urine? I believe we shall soon be able to answer in the affirmative. May I be permitted to indicate what I think to be the probable constructive lines. On the one hand, we may believe that the glomerulus excretes water, urea, chlorides, and possibly other salts, and that it must be so delicately adjusted as to respond to very small variations in the amounts of these substances in the blood and have a selective excretory activity for each substance, which may be either increased or decreased by disease, etc. Sulphates and phosphates may be added by the tubules with such other substances as the urates. It may even be that each constituent is added by a different secreting mechanism. It might also be suggested that the excretory activity regulated the amount and distribution of the blood flow. On the other hand, the researches of Kahlenberg may lead us to a new physical conception of semipermeable membranes, and of diffusion, and may thus open up for us entirely new conceptions in regard to animal membranes and the role that osmosis plays within the body.

I feel myself unfortunate that in this review of the kidney's functions I have not been able to indicate in any way the probable cause and method of the treatment of uremia.

The futility of trying to form soluble compounds of uric acid, and so aid its being washed out of the kidney, seems to me to be disclosed in the above. Even the highly soluble piperazin compound, or, as shown by Nicolaier lately, the formaldehyde compound, are not excreted as such, but are broken down and excreted as less soluble urates. Probably any beneficial action that piperazin had was due to its action in dilating the kidney vessels and so increasing the blood flow through the kidney.

That digitalin and the purin bodies at times fail is not astonishing when one considers that neither causes a specific secretion, but their action is limited by the state of the bloodstream and its richness or poorness in water.

Further, the inability and failure of digitalis and of caffeine to cause diuresis even in œdema, when salt retention is present, is abundantly evident. It is in those cases that decreased in salt intake has given such astonishing results.

That salines, acetates, and sulphates, etc., act as diuretics when caffeine and calomel fail, is not astonishing when one realizes the changes in blood and in composition of urine which occur when they are exhibited. That they may fail when caffeine is efficient is equally lacking in peculiarity.

Most important of all, I think, is the fact that with our lack of knowledge of the kidney, and how it carries on its function, it is not to be expected that we will be successful, as indeed we are not, in forcing the kidney to excrete when it is diseased. The fact that when there is chloride retention an increased intake may cause more marked retention, taken altogether with the facts mentioned above, that Riedel, Brandenstein and Achard have shown that undue amounts of water cause damage to the kidney, as does excretion of undue amounts of salts, as shown by Leopold, should lead us, especially in nephritis, to guard the kidneys from labor of every kind that can be avoided.